Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial

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Summary

Background There are no systemic treatments for patients with hepatocellular carcinoma (HCC) whose disease progresses during sorafenib treatment. We aimed to assess the efficacy and safety of regorafenib in patients with HCC who have progressed during sorafenib treatment.

Methods In this randomised, double-blind, parallel-group, phase 3 trial done at 152 sites in 21 countries, adults with HCC who tolerated sorafenib (≥400 mg/day for ≥20 of last 28 days of treatment), progressed on sorafenib, and had Child-Pugh A liver function were enrolled. Participants were randomly assigned (2:1) by a computer-generated randomisation list and interactive voice response system and stratified by geographical region, Eastern Cooperative Oncology Group performance status, macrovascular invasion, extrahepatic disease, and α-fetoprotein level to best supportive care plus oral regorafenib 160 mg or placebo once daily during weeks 1–3 of each 4-week cycle. Investigators, patients, and the funder were masked to treatment assignment. The primary endpoint was overall survival (defined as time from randomisation to death due to any cause) and analysed by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01774344.

Findings Between May 14, 2013, and Dec 31, 2015, 843 patients were screened, of whom 573 were enrolled and randomised (379 to regorafenib and 194 to placebo; population for efficacy analyses), and 567 initiated treatment (374 received regorafenib and 193 received placebo; population for safety analyses). Regorafenib improved overall survival with a hazard ratio of 0·63 (95% CI 0·50–0·79; one-sided p<0·0001); median survival was 10·6 months (95% CI 9·1–12·1) for regorafenib versus 7·8 months (6·3–8·8) for placebo. Adverse events were reported in all regorafenib recipients (374 [100%] of 374) and 179 (93%) of 193 placebo recipients. The most common clinically relevant grade 3 or 4 treatment-emergent events were hypertension (57 patients [15%] in the regorafenib group *vs* nine patients [5%] in the placebo group), hand–foot skin reaction (47 patients [13%] *vs* one [1%]), fatigue (34 patients [9%] *vs* nine patients [5%]), and diarrhoea (12 patients [3%] *vs* no patients). Of the 88 deaths (grade 5 adverse events) reported during the study (50 patients [13%] assigned to regorafenib and 38 [20%] assigned to placebo), seven (2%) were considered by the investigator to be related to study drug in the regorafenib group and two (1%) in the placebo group, including two patients (1%) with hepatic failure in the placebo group.

Interpretation Regorafenib is the only systemic treatment shown to provide survival benefit in HCC patients progressing on sorafenib treatment. Future trials should explore combinations of regorafenib with other systemic agents and third-line treatments for patients who fail or who do not tolerate the sequence of sorafenib and regorafenib.

Funding Bayer.

Introduction

The treatment of hepatocellular carcinoma (HCC) follows well established guidelines.[1–3] Surgical resection, transplantation, and ablation are potential curative options for early-stage disease, whereas chemoembolisation is recommended for patients with preserved liver function and disease confined to the liver generally without vascular invasion. For patients who are not or who are no longer candidates for locoregional therapy, the oral multikinase inhibitor sorafenib is the only systemic treatment shown to provide a clinically significant improvement in overall survival.[4,5] Since the results with sorafenib were published almost 10 years ago, all phase 3 trials assessing novel systemic drugs have failed to improve outcomes over sorafenib in the first-line setting[6–10] or in the second-line setting following sorafenib.[11–14] In second-line trials in patients who have failed sorafenib, overall survival in the placebo group is about 8 months.[11–14] Therefore, there is an unmet need for effective systemic therapies for HCC, particularly after treatment with sorafenib.

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed for articles published between Jan 1, 2008, and Oct 26, 2016, with no language restrictions, reporting on the treatment of patients with advanced hepatocellular carcinoma (HCC) who failed sorafenib treatment using the search terms ("advanced hepatocellular carcinoma" OR "advanced hepatocellular cancer") AND "sorafenib", filtering for articles describing phase 3 clinical trials. We also searched abstracts of the annual meeting of the American Society of Clinical Oncology, using the search term "advanced hepatocellular carcinoma", limiting the results to phase 3 trials published or presented during the past 2 years. The search resulted in 15 articles or abstracts, of which three were excluded (two subanalyses and one report of maintenance sorafenib therapy following the combination of transcatheter arterial chemoembolisation and radiotherapy). Of the remaining 12 publications, two were reports of the pivotal trials of sorafenib for advanced HCC; five reported the first-line use of a novel drug or the novel combination of a drug with sorafenib compared with a sorafenib control; and five reported the second-line use of a novel agent in patients who had failed sorafenib. None of the trials assessing novel agents or novel combinations of agents in the first-line setting met the primary endpoint to show improved overall survival over sorafenib. Similarly, none of the drugs assessed in the second-line setting in patients previously treated with sorafenib who stopped because of disease progression or intolerance showed improvement over placebo. Therefore, new effective systemic therapies for patients with advanced HCC who fail sorafenib treatment are needed.

Added value of this study

Until now, no systemic agent has been shown to improve survival over placebo in patients with advanced HCC who fail sorafenib treatment. The results of RESORCE show that treatment with regorafenib resulted in a significant improvement in overall survival compared with placebo in patients with disease progression on sorafenib. Significant improvement over placebo was also shown for the secondary endpoints of progression-free survival, time to progression, disease control, and overall tumour response.

Implications of all the available evidence

This phase 3 trial of regorafenib is the first to show an overall survival benefit compared with placebo in patients who failed sorafenib treatment. Future trials should explore combinations of regorafenib with other systemic agents and third-line treatments for patients who fail or who do not tolerate the sequence of sorafenib and regorafenib.

Regorafenib is an oral multikinase inhibitor that blocks the activity of protein kinases involved in angiogenesis, oncogenesis, metastasis, and tumour immunity.[15,16] It has a distinct molecular target profile and had more potent pharmacological activity than sorafenib in preclinical studies.[15,17] Regorafenib is approved as monotherapy for the treatment of treatment-refractory metastatic colorectal cancer and gastrointestinal stromal tumours at a dose of 160 mg once daily for the first 3 weeks of each 4-week cycle.[18–20] Based on results of a single-arm phase 2 study showing antitumour activity and acceptable tolerability,[21] we aimed to assess the efficacy and safety of regorafenib in patients with HCC who progressed during sorafenib treatment.

Methods

Study design and participants

This randomised, double-blind, placebo-controlled international phase 3 trial was done at 152 centres in 21 countries in North America, South America, Europe, Asia, and Australia.

Eligible patients were adults with HCC confirmed by pathological assessment or non-invasive assessment according to the American Association for the Study of Liver Diseases criteria for patients with confirmed cirrhosis,[1] and had to have at least one measurable lesion by modified Response Evaluation Criteria in Solid Tumors for HCC (mRECIST)[22] and RECIST version 1.1. Patients were Barcelona Clinic Liver Cancer (BCLC) stage B or C,[23] could not benefit from resection, local ablation, or chemoembolisation, and must have had documented radiological progression during sorafenib treatment as defined in a study-specific radiology charter. They must have tolerated sorafenib (≥400 mg daily for at least 20 of the 28 days before discontinuation) and received their last sorafenib dose within 10 weeks of randomisation. They were required to have Child-Pugh A liver function. Patients were excluded if they had received any other previous systemic treatment for HCC or if they discontinued sorafenib for toxicity (see appendix pp 5–7 for full inclusion and exclusion criteria).

All patients provided written informed consent. The trial was approved by each centre's ethics committee or institutional review board and complied with Good Clinical Practice guidelines, the Declaration of Helsinki, and applicable local laws.

Randomisation and masking

Patients were randomly assigned (2:1) to regorafenib or placebo using a computer-generated randomisation list prepared by the funder. Randomisation was stratified by geographical region (Asia *vs* rest of world), macrovascular invasion (yes *vs* no), extrahepatic disease (yes *vs* no), α-fetoprotein concentration (<400 ng/mL *vs* ≥400 ng/mL), and Eastern Cooperative Oncology Group (ECOG) performance status (0 *vs* 1). The proportion of patients recruited from Asia was limited to 40%. Investigators, patients, and the funder were masked to treatment

assignment. The randomisation number for each patient was assigned based on information obtained from the interactive voice-response system. Tablets with identical appearance were used for regorafenib and placebo.

Procedures

Patients received 160 mg regorafenib (four 40 mg tablets) orally or matching placebo once daily for the first 3 weeks of each 4-week cycle. All patients received best supportive care. Other investigational antitumour drugs, antineoplastic chemotherapy, hormonal therapy, or immunotherapy were not allowed. Treatment continued until disease progression as defined by mRECIST, clinical progression (defined as an ECOG performance score ≥3 or symptomatic deterioration, including increased liver function tests), death, unacceptable toxicity, withdrawal of consent by the patient, or decision by the treating physician that discontinuation would be in the patient's best interest. Patients were followed up for tumour assessments every 6 weeks for the first eight cycles and every 12 weeks thereafter during treatment. Treatment could be continued beyond progression if the investigator judged that the patient would benefit from continued treatment. Patients assigned to placebo could receive regorafenib after the primary analysis.

Treatment interruptions and dose reductions (to 120 mg, then 80 mg) were allowed to manage toxicity (appendix pp 12–15). The regorafenib dose could be re-escalated to a maximum of 160 mg at the investigator's discretion once toxicities were resolved. If further dose reduction was required, treatment was discontinued.

Outcomes

The primary endpoint was overall survival (time from randomisation to death due to any cause), analysed by intention to treat (ITT). Secondary efficacy endpoints were progression-free survival (randomisation to radiological or clinical disease progression or death; by ITT), time to progression (randomisation to radiological or clinical disease progression; by ITT), objective response rate (patients with complete or partial response), and disease control rate (patients with complete response, partial response, or stable disease maintained for ≥6 weeks), assessed by investigators using mRECIST[22] and RECIST 1.1 (appendix p 7).

Health-related quality of life (HRQoL) was a teritiary outcome assessed using the Functional Assessment of Cancer Therapy (FACT)–General (FACT-G), FACT–Hepatobiliary (FACT-Hep), EQ-5D, and EQ-VAS questionnaires.[24,25] The following tertiary endpoints are not reported here: pharmacokinetics of regorafenib, and biomarker evaluation. Safety was assessed by adverse events, laboratory abnormalities, vital signs, and electrocardiography. Safety was monitored continuously throughout the study, and patients underwent safety evaluations at every cycle. Concentrations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin were assessed weekly during the first two cycles. Adverse events were graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 (appendix p 7 for further assessments) and seriousness of adverse events was recorded. Investigators were blinded to study treatment for assessment of whether a death was considered related to study drug.

Statistical analysis

Using a per-protocol one-sided α of 0·025, a 2:1 randomisation between regorafenib and placebo, and assuming a median overall survival of 8 months in the placebo group, the study would have 90% power to detect a 43% increase in overall survival with regorafenib (assumed median survival 11·4 months) compared with placebo at 370 deaths and requiring 560 patients. For the primary efficacy endpoint of overall survival, the groups were compared using a log-rank test, stratified by the

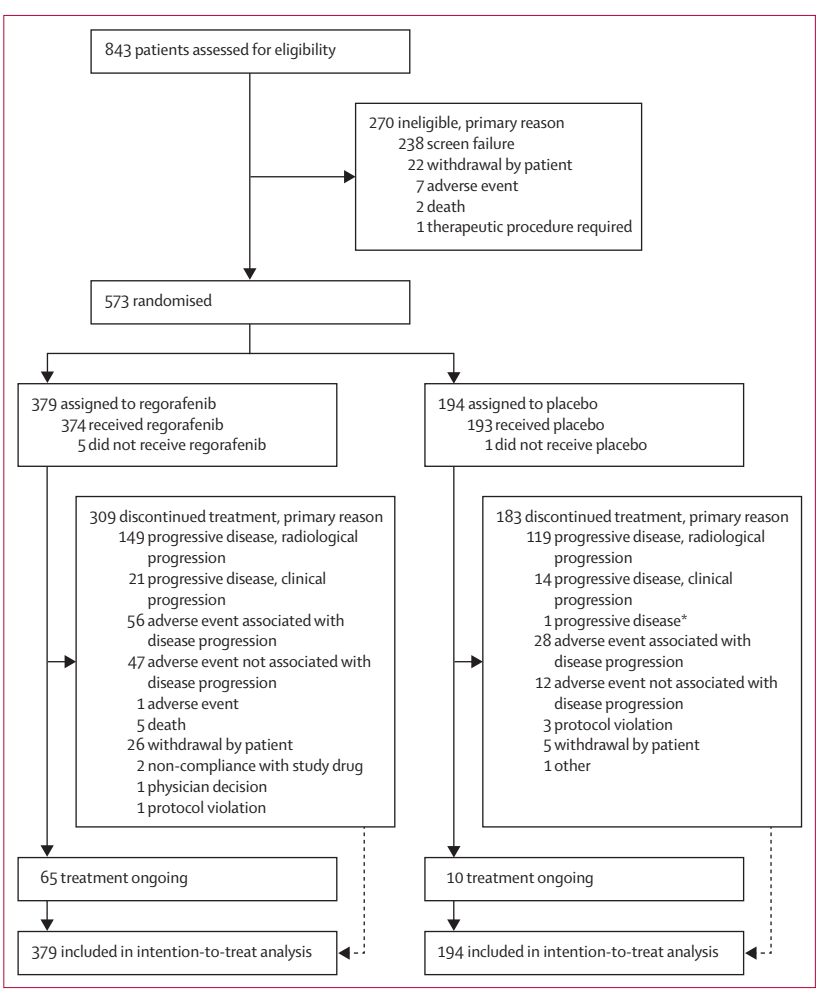


***Figure 1*: Trial profile**

*Patient had radiological progression but continued treatment, and terminated treatment when the investigator judged that the patient was no longer experiencing clinical benefit.

	Regorafenib (n=379)	Placebo (n=194)
Sex		
Male	333 (88%)	171 (88%)
Female	46 (12%)	23 (12%)
Age, years	64 (54–71)	62 (55–68)
Race		
White	138 (36%)	68 (35%)
Asian	156 (41%)	78 (40%)
Black	6 (2%)	2 (1%)
Other/not reported	79 (21%)	46 (24%)
Geographical region		
Rest of world	236 (62%)	121 (62%)
Asia*	143 (38%)	73 (38%)
ECOG performance status		
0	247 (65%)	130 (67%)
1	132 (35%)	64 (33%)
Macrovascular invasion	110 (29%)	54 (28%)
Extrahepatic disease	265 (70%)	147 (76%)
Macrovascular invasion and/or extrahepatic disease	304 (80%)	162 (84%)
Lung, target lesion†	98 (26%)	48 (25%)
Lymph node, target lesion†	58 (15%)	36 (19%)
Lung, non-target lesion†	121 (32%)	57 (29%)
Lymph node, non-target lesion†	61 (16%)	29 (15%)
Pattern of progression on previous sorafenib treatment		
New extrahepatic lesion	153 (40%)	80 (41%)
New intrahepatic lesion	168 (44%)	88 (45%)
Growth of intrahepatic or extrahepatic lesions, or both	307 (81%)	156 (80%)
α-fetoprotein ≥400 ng/mL	162 (43%)	87 (45%)
Child-Pugh class‡		
A	373 (98%)	188 (97%)
B	5 (1%)	6 (3%)
BCLC stage		
A (early)	1 (<1%)	0
B (intermediate)	53 (14%)	22 (11%)
C (advanced)	325 (86%)	172 (89%)
(Continued from previous column)		
Liver cirrhosis (investigator assessed)	285 (75%)	144 (74%)
Aetiology of HCC§		
Hepatitis B	143 (38%)	73 (38%)
Alcohol use	90 (24%)	55 (28%)
Hepatitis C	78 (21%)	41 (21%)
Unknown	66 (17%)	32 (16%)
Non-alcoholic steatohepatitis	25 (7%)	13 (7%)
Other	28 (7%)	10 (5%)
Number of target lesions (mRECIST)¶		
1	67 (18%)	31 (16%)
2	175 (46%)	88 (45%)
3	68 (18%)	37 (19%)
4	43 (11%)	26 (13%)
5	19 (5%)	12 (6%)
Time from initial HCC diagnosis to start of study treatment, months		
Median (IQR)	21 (11–38)	20 (12–32)
Mean (SD)	29 (28)	27 (22)
Duration of sorafenib treatment, months	7·8 (4·2–14·5)	7·8 (4·4–14·7)
Time from progression on sorafenib to start of study treatment, months	1·4 (0·9–2·3)	1·4 (0·9–2·2)
Time from discontinuation of sorafenib to start of study treatment, months	0·9 (0·7–1·3)	0·9 (0·7–1·3)

Data are n (%) or median (IQR), unless otherwise specified. BCLC=Barcelona Clinic Liver Cancer. ECOG=Eastern Cooperative Oncology Group. HCC=hepatocellular carcinoma. mRECIST=modified RECIST for HCC. *Includes patients from China, Japan, South Korea, Singapore, and Taiwan. †RECIST version 1.1. ‡The Child-Pugh system describes liver disease severity: patients are divided into classes from A to C, with class C representing the worst prognosis. Child-Pugh class was missing in one patient in the regorafenib group. Those patients who progressed to Child-Pugh B after screening and before randomisation were included. §Patients could have more than one aetiology of HCC. ¶n=372 in the regorafenib group.

Table 1: **Baseline characteristics (efficacy population)**

aforementioned randomisation factors. The hazard ratio (HR) for overall survival and its 95% CI were calculated using the stratified Cox model. An interim futility analysis was done after 30% of the events had occurred; futility boundaries were not crossed. For analyses of time to progression and progression-free survival, groups were compared using a log-rank test stratified by the factors used in the analyses of the primary endpoint. The response rates and disease control rates in the two groups were compared using the Cochran–Mantel–Haenszel test, with adjustment for the stratification factors.

For HRQoL assessments, an analysis-of-covariance model was used to compare the time-adjusted area under the curve (AUC) between groups with covariates for baseline scores and stratification factors. The least-squares mean (LSM) with 95% CI was estimated for each treatment group and for the difference between groups.

Data were analysed with SAS, version 9.2 (SAS Institute Inc, Cary, NC, USA). The primary analysis was by intention to treat; safety analyses included all patients who received at least one dose of study drug. The study was overseen by a data safety monitoring committee.

This trial is registered with ClinicalTrials.gov, number NCT01774344.

Role of the funding source
The funder (Bayer) provided the study drug and worked with the principal investigator (JB) and the study steering committee to design the study. Data collection and interpretation, and preparation of this report, were done by the investigators and the funder. Statistical analyses were performed by the funder. All authors reviewed this report and approved the submission for publication, had full access to the data, and vouch for the completeness and accuracy of the data and adherence of the study to the protocol. The funder funded writing assistance.

Results

Between May 14, 2013, and Dec 31, 2015, 843 patients were screened, of whom 573 were enrolled and randomised (379 to regorafenib and 194 to placebo; population for efficacy analyses; figure 1). 216 patients (38%) were from Asia. Overall, 567 patients (99%) started treatment (374 in the regorafenib group and 193 in the placebo group) and comprise the safety analysis population. Treatment groups were similar with respect to baseline demographics, tumour burden, ECOG performance status, aetiology, and severity of liver disease (table 1). We also assessed the pattern of progression during sorafenib treatment because this parameter has been shown to influence outcomes and could distort the results of second-line studies.[26] A potential imbalance in the pattern of progression on previous sorafenib was ruled out because the distribution of the different categories was similar across the treatment groups. Specifically, the development of new extrahepatic sites during previous sorafenib, which was recently shown to be associated with a worse prognosis,[26] was present in 153 (40%) patients in the regorafenib group and 80 (41%) in the placebo group. Similarly, growth of existing lesions (intrahepatic or extrahepatic; 307 [81%] patients in the regorafenib group and 156 [80%] patients in the placebo group) or new intrahepatic sites (168 [44%] patients in the regorafenib group and 88 [45%] patients in the placebo group) were balanced between treatment groups.

Median time on sorafenib was 7·8 months (IQR 4·2–14·5) in the regorafenib group and 7·8 months (4·4–14·7) in the placebo group. Median time from progression on sorafenib was similar in both groups (1·4 months [IQR 0·9–2·3] in the regorafenib group *vs* 1·4 months [0·9–2·2] in the placebo group), as was the median time from discontinuation of sorafenib to the start of study treatment (0·9 months [IQR 0·7–1·3] in both groups).

Of patients who started treatment, 309 (83%) receiving regorafenib and 183 (95%) receiving placebo discontinued study treatment (figure 1). The most common reason for discontinuation was disease progression (226 [60%] in the regorafenib group and 162 [84%] in the placebo group). Median treatment duration was 3·6 months (IQR 1·6–7·6) with regorafenib and 1·9 months (1·4–3·9) with placebo; mean durations were 5·9 months (SD 6·0) and 3·3 months (3·9), respectively. Mean daily dose of regorafenib was 144·1 mg (SD 21·3) and of placebo was 157·4 mg (10·3). Excluding treatment delays or interruptions, almost half of the regorafenib group (184 [49%] of 374]) received the full protocol dose (160 mg/day) with no reductions.

At the cutoff date for the final analysis (Feb 29, 2016) and a median follow-up of 7·0 months (IQR 3·7–12·6),

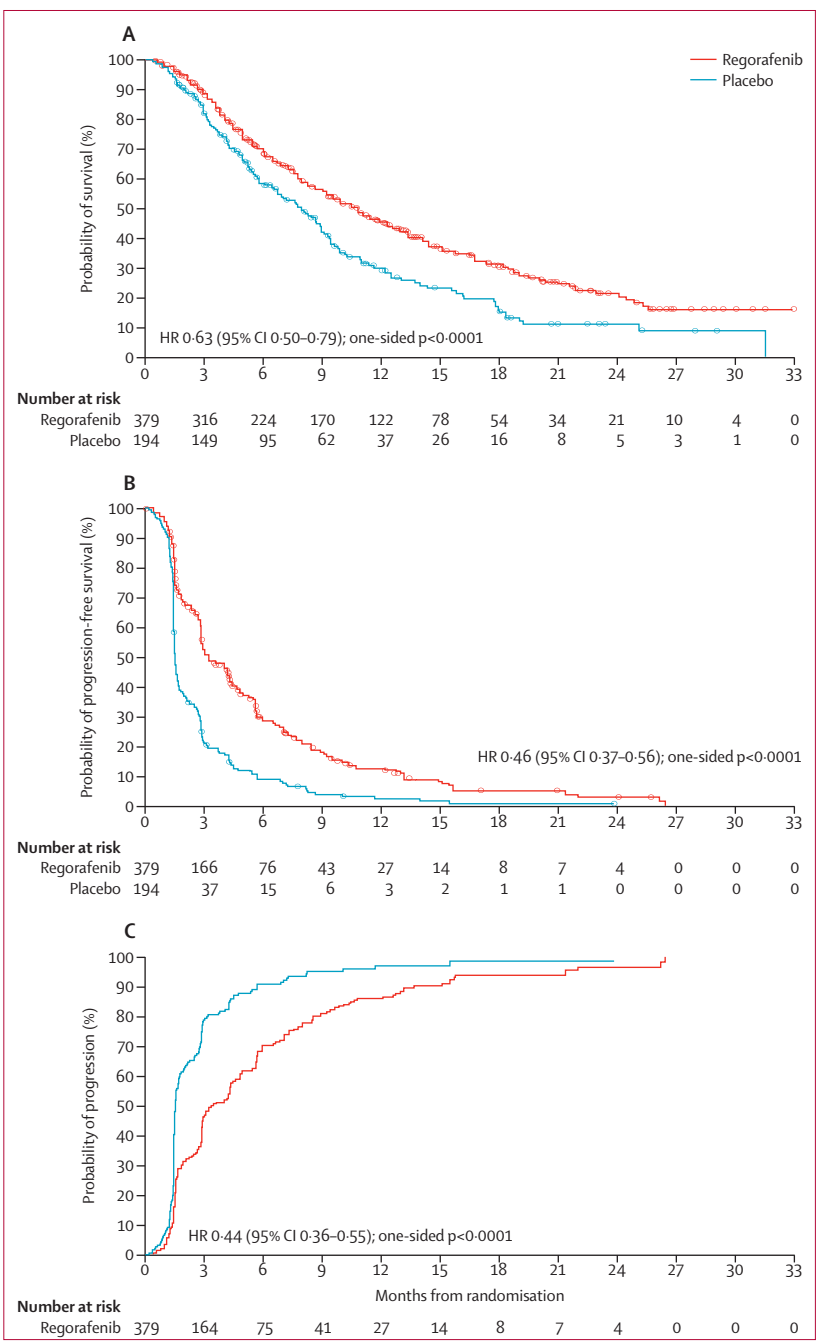
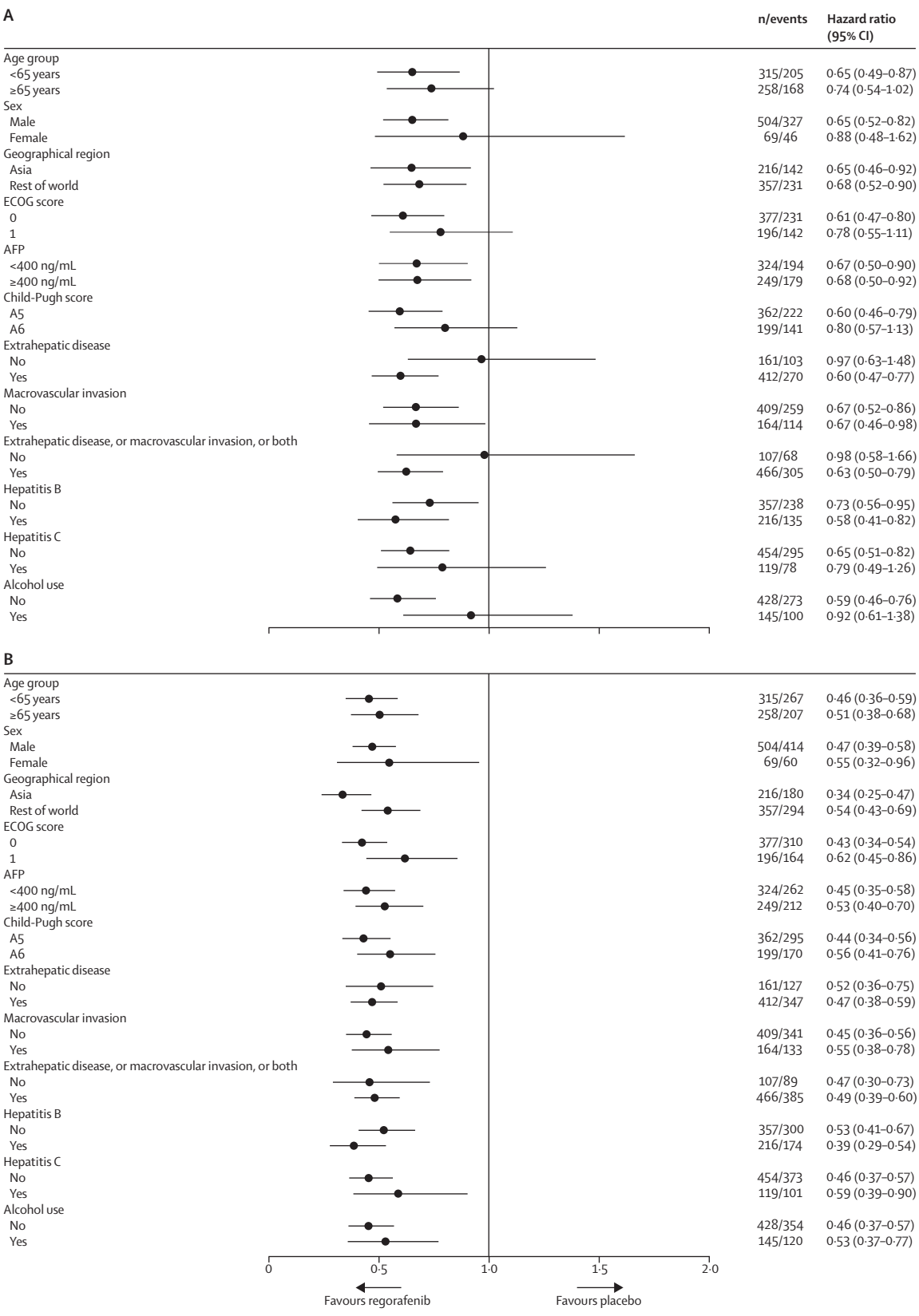


Figure 2: **Kaplan-Meier analysis of overall survival (A), progression-free survival (mRECIST; B), and time to progression (mRECIST; C)**
mRECIST=modified RECIST for hepatocellular carcinoma.



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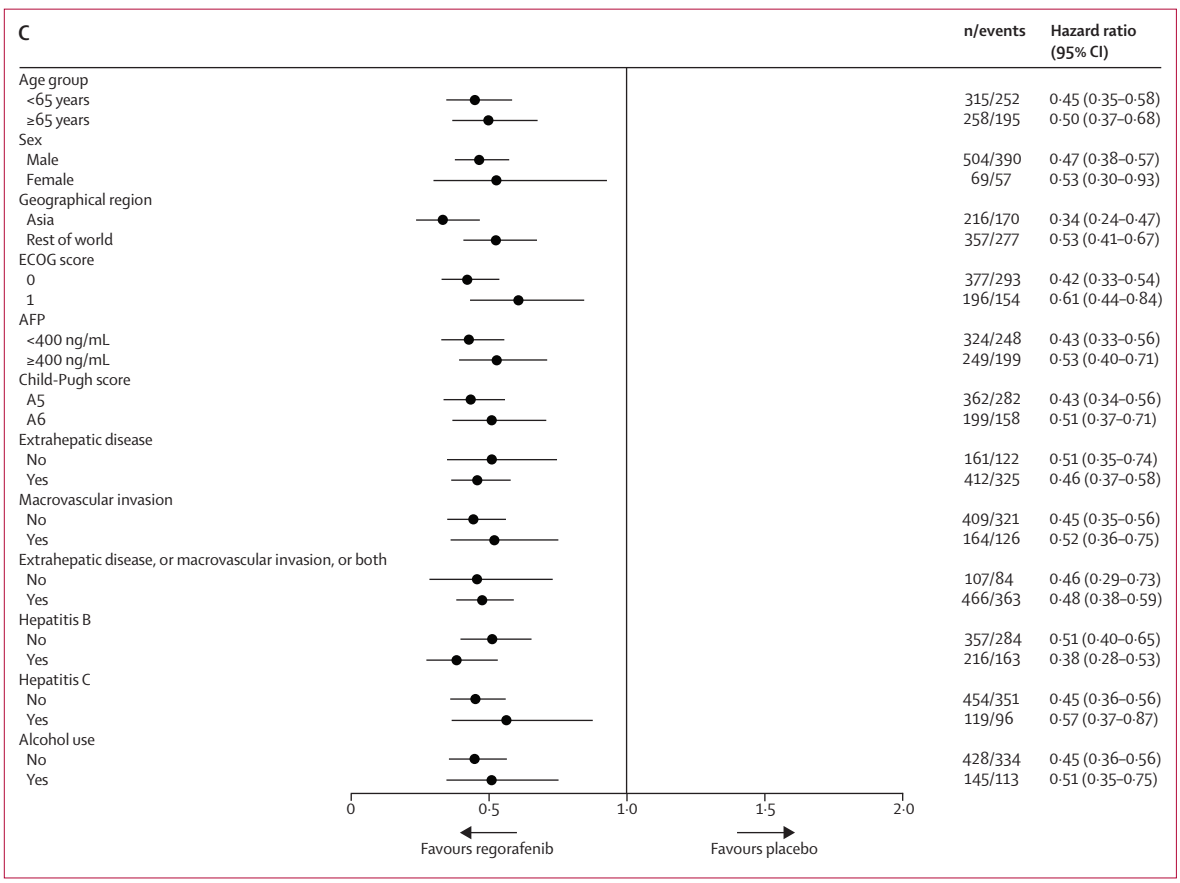

Figure 3: **Overall survival (A), progression-free survival (mRECIST; B), and time to progression (mRECIST; C) in selected subgroups**
AFP=α-fetoprotein. ECOG=Eastern Cooperative Oncology Group. mRECIST=modified RECIST.

373 (65%) of the 573 randomised patients had died (233 [61%] of 379 in the regorafenib group and 140 [72%] of 194 in the placebo group). Median overall survival was 10·6 months (95% CI 9·1–12·1) with regorafenib and 7·8 months (6·3–8·8) with placebo (HR 0·63 [95% CI 0·50–0·79]; one-sided p<0·0001; figure 2A). The improvement in overall survival with regorafenib was maintained in all preplanned subgroup analyses (figure 3A; appendix p 16).

Median progression-free survival by mRECIST was 3·1 months (95% CI 2·8–4·2) with regorafenib and 1·5 months (1·4–1·6) with placebo (figure 2B). Median time to progression by mRECIST was 3·2 months (95% CI 2·9–4·2) with regorafenib and 1·5 months (1·4–1·6) with placebo (figure 2C). Predefined subgroup analysis for progression-free survival and time to progression also showed a consistent benefit (figures 3B,C). The HRs for progression-free survival and time to progression assessed by RECIST 1.1 were comparable (appendix pp 8–11).

Two patients (1% [95% CI <1–2]) in the regorafenib group versus no patients in the placebo group had a complete response and 38 patients (10% [7–14]) in the regorafenib group versus eight patients (4% [2–8]) in the placebo group had a partial response by mRECIST as assessed by investigators (table 2). 40 (11%) of 379 patients in the regorafenib group versus eight (4%) of 194 patients in the placebo group achieved an objective response (p=0·0047). 247 (65%) of 379 patients in the regorafenib group versus 70 (36%) of 194 patients in the placebo group achieved disease control (p<0·0001). A significant improvement in tumour response and disease control was also shown using RECIST 1.1 (appendix p 16). Tumour shrinkage (any decrease in the sum of diameters of target lesions) was reported in 49% (184/379) of patients in the regorafenib group and 23% (44/194) of patients in the placebo group (appendix p 17). Duration of response and duration of stable disease are reported in the appendix (p 17).

All (374/374) patients who received regorafenib and 179 (93%) of 193 patients who received placebo had at least one treatment-emergent adverse event; these were deemed possibly study-drug related in 346 (93%) patients who received regorafenib and 100 (52%) patients who received placebo (table 3). The most common clinically relevant grade 3 or 4 events were hypertension (57 patients [15%] in

	Regorafenib (n=379)	Placebo (n=194)
Best overall response*		
Complete response	2 (1%; <1–2)	0
Partial response	38 (10%; 7–14)	8 (4%; 2–8)
Stable disease	206 (54%; 49–59)	62 (32%; 26–39)
Non-complete response/ non-progressive disease	1 (<1%; 0–2)	0
Progressive disease	86 (23%; 19–27)	108 (56%; 48–63)
Not evaluable	19 (5%; 3–8)	8 (4%; 2–8)]
Not assessed	27 (7%; 5–10)	8 (4%; 2–8)
Clinical progression†	86 (23%; 19–27)	40 (21%; 15–27)
Objective response (complete response + partial response)*	40 (11%)‡	8 (4%)‡
Disease control*	247 (65%)§	70 (36%)§

Data are n (%; 95% CI). *Based on radiological review using modified Response Evaluation Criteria in Solid Tumors for HCC (mRECIST).[22] †Defined as worsening of ECOG performance status or symptomatic deterioration including increase in liver function tests. ‡One-sided p=0·0047. §One-sided p<0·0001.

Table 2: **Tumour response (efficacy population)**

the regorafenib group *vs* nine patients [5%] in the placebo group), hand–foot skin reaction (47 patients [13%] *vs* one [1%]), fatigue (34 patients [9%] *vs* nine patients [5%]), and diarrhoea (12 patients [3%] *vs* no patients). The frequency of hepatobiliary disorders was higher with placebo (18% [34/193]) than with regorafenib (11% [40/374]). Serious adverse events occurred in 166 (44%) patients assigned to regorafenib and 90 (47%) patients assigned to placebo and were attributed to study drug in 39 (10%) patients assigned to regorafenib and five (3%) patients assigned to placebo. Of the 88 deaths (grade 5 adverse events) reported during the study (50 patients [13%] assigned to regorafenib and 38 [20%] assigned to placebo), seven (2%) were considered by the investigator to be related to study drug in the regorafenib arm and two (1%) in the placebo arm, including two patients (1%) with hepatic failure in the placebo group (appendix p 18). 21 (6%) of 374 patients in the regorafenib group had grade 3 or higher treatment-emergent bleeding events versus 15 (8%) of 193 patients in the placebo group (appendix p 18). 255 (68%) of 374 patients in the regorafenib group had interruptions or dose reductions due to adverse events versus 60 (31%) of 193 patients in the placebo group. Similarly, 93 (25%) of 374 patients in the regorafenib group discontinued due to adverse events versus 37 (19%) of 193 patients in the placebo group. Drug-related adverse events led to interruptions or dose reductions in 202 (54%) patients in the regorafenib group and 20 (10%) patients in the placebo group, and to discontinuations in 39 (10%) patients in the regorafenib group and seven (4%) patients in the placebo group. The most common adverse events leading to discontinuation more frequently with regorafenib were increase in AST concentration (eight [2%] of 374 patients in the regorafenib group *vs* three [2%] of 193 patients in the placebo group), hand–foot skin reaction (seven [2%] *vs* none), and ALT increase (four [1%] *vs* none).

No clinically meaningful differences were noted between the regorafenib and placebo groups in HRQoL. Overall changes from baseline in EQ-5D and FACT-Hep were similar in the two groups. In the LSM time-adjusted AUC analysis of the EQ-5D and FACT-Hep, the scores were lower in the regorafenib group than in the placebo group, and specifically the scores of the FACT-Hep Total and Trial Outcome Index (a subscale of the FACT-Hep) were statistically lower in the regorafenib group than in the placebo group (p=0·0006 and p<0·0001, respectively); however, minimally important thresholds for the differences as established in the literature were not met (appendix p 19).[24,25]

Discussion

Our study shows that regorafenib provides a significant and clinically meaningful improvement in overall survival in patients with HCC progressing during sorafenib treatment. This finding was associated with an increase in median survival from 7·8 months to 10·6 months. This survival benefit was maintained in the prespecified subgroup analyses, including geographical region and aetiology, and was accompanied by significant improvements in progression-free survival, time to progression, and objective response, and disease control rate. Two patients treated with regorafenib had a complete tumour response by mRECIST, which excludes necrosis of the target lesion from the tumour measurement. These responses would also have been classified as complete using conventional European Association for the Study of the Liver criteria.[27] Interestingly, we noted similar outcomes using mRECIST and RECIST 1.1 for progression-free survival and time to progression.

The survival of the placebo group in our study is consistent with previous second-line studies in HCC at about 8 months.[11–14] Use of five stratification factors ensured that the trial groups were fully balanced for commonly assessed patient and disease characteristics; however, we also analysed the distribution of patients across treatment groups according to the pattern of progression under sorafenib. Pattern of progression has recently been found to be a major factor affecting outcome and potentially confounding study results if not balanced across study groups.[26] Although new intrahepatic sites or growth of known tumour lesions have been shown to have a moderate effect on post-progression survival, the development of new vascular invasion or extrahepatic spread is a significant predictor of a worse survival.[26] Pattern of progression under previous sorafenib was balanced in this study.

All primary and secondary efficacy outcomes in this sorafenib pretreated population seem numerically better than those with sorafenib in the first-line setting.[4,5] This might be because regorafenib is more pharmacologically

	Treatment-emergent						Treatment-emergent drug-related					
	Regorafenib (n=374)			Placebo (n=193)			Regorafenib (n=374)			Placebo (n=193)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Any adverse event	374 (100%)	208 (56%)	40 (11%)	179 (93%)	61 (32%)	14 (7%)	346 (93%)	173 (46%)	14 (4%)	100 (52%)	31 (16%)	1 (1%)
Hand–foot skin reaction	198 (53%)	47 (13%)	NA	15 (8%)	1 (1%)	NA	196 (52%)	47 (13%)	NA	13 (7%)	1 (1%)	NA
Diarrhoea	155 (41%)	12 (3%)	0	29 (15%)	0	0	125 (33%)	9 (2%)	0	18 (9%)	0	0
Fatigue	151 (40%)	34 (9%)	NA	61 (32%)	9 (5%)	NA	110 (29%)	24 (6%)	NA	37 (19%)	3 (2%)	NA
Hypertension	116 (31%)	56 (15%)	1 (<1%)	12 (6%)	9 (5%)	0	87 (23%)	48 (13%)	1 (<1%)	9 (5%)	6 (3%)	0
Anorexia	116 (31%)	10 (3%)	0	28 (15%)	4 (2%)	0	88 (24%)	10 (3%)	0	12 (6%)	0	0
Increased blood bilirubin	108 (29%)	37 (10%)	2 (1%)	34 (18%)	15 (8%)	6 (3%)	70 (19%)	24 (6%)	1 (<1%)	7 (4%)	4 (2%)	0
Abdominal pain	105 (28%)	13 (3%)	NA	43 (22%)	8 (4%)	NA	34 (9%)	5 (1%)	NA	5 (3%)	0	NA
Increased AST	92 (25%)	37 (10%)	4 (1%)	38 (20%)	19 (10%)	3 (2%)	48 (13%)	16 (4%)	3 (1%)	15 (8%)	9 (5%)	1 (1%)
Fever	72 (19%)	0	0	14 (7%)	0	0	14 (4%)	0	0	4 (2%)	0	0
Nausea	64 (17%)	2 (1%)	NA	26 (13%)	0	NA	40 (11%)	1 (<1%)	NA	13 (7%)	0	NA
Constipation	65 (17%)	1 (<1%)	0	22 (11%)	1 (1%)	0	24 (6%)	0	0	3 (2%)	0	0
Ascites	58 (16%)	16 (4%)	0	31 (16%)	11 (6%)	0	8 (2%)	3 (1%)	0	1 (1%)	1 (1%)	0
Anaemia	58 (16%)	16 (4%)	2 (1%)	22 (11%)	10 (5%)	1 (1%)	23 (6%)	5 (1%)	1 (<1%)	2 (1%)	1 (1%)	0
Limb oedema	60 (16%)	2 (1%)	NA	24 (12%)	0	NA	12 (3%)	1 (<1%)	NA	1 (1%)	0	NA
Increased ALT	55 (15%)	10 (3%)	2 (1%)	22 (11%)	5 (3%)	0	29 (8%)	6 (2%)	2 (1%)	8 (4%)	2 (1%)	0
Hypoalbuminaemia	57 (15%)	6 (2%)	0	16 (8%)	1 (1%)	0	9 (2%)	2 (1%)	0	0	0	0
General disorders and administration site conditions, other	53 (14%)	16 (4%)	2 (1%)	29 (15%)	6 (3%)	3 (2%)	8 (2%)	5 (1%)	0	2 (1%)	1 (1%)	0
Weight loss	51 (14%)	7 (2%)	NA	9 (5%)	0	NA	27 (7%)	4 (1%)	NA	3 (2%)	0	NA
Oral mucositis	47 (13%)	4 (1%)	0	6 (3%)	1 (1%)	0	42 (11%)	4 (1%)	0	5 (3%)	1 (1%)	0
Vomiting	47 (13%)	3 (1%)	0	13 (7%)	1 (1%)	0	27 (7%)	1 (<1%)	0	5 (3%)	0	0
Investigations, other	40 (11%)	4 (1%)	0	11 (6%)	1 (1%)	0	18 (5%)	1 (<1%)	0	0	0	0
Back pain	42 (11%)	6 (2%)	1 (<1%)	17 (9%)	2 (1%)	0	2 (1%)	1 (<1%)	0	2 (1%)	0	0
Thrombocytopenia	39 (10%)	13 (3%)	1 (<1%)	5 (3%)	0	0	19 (5%)	7 (2%)	1 (<1%)	2 (1%)	0	0
Cough	40 (11%)	1 (<1%)	NA	14 (7%)	0	NA	4 (1%)	0	NA	2 (1%)	0	NA
Hypophosphataemia	37 (10%)	30 (8%)	2 (1%)	4 (2%)	3 (2%)	0	22 (6%)	16 (4%)	2 (1%)	2 (1%)	1 (1%)	0
Hoarseness	39 (10%)	0	NA	1 (1%)	0	NA	34 (9%)	0	NA	0	0	NA

Data are n (%). Adverse events were graded using NCI-CTCAE version 4.03. ALT=alanine aminotransferase. AST=aspartate aminotransferase. NA=not applicable. NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events. *Events listed are treatment-emergent adverse events occurring in at least 10% of patients in either treatment group.

Table 3: **Treatment-emergent adverse events and treatment-emergent drug-related adverse events* (safety population)**

active than is sorafenib,[15] and could also be because tolerability to regorafenib was improved for patients tolerant to sorafenib due to the somewhat overlapping adverse-event profiles of the two drugs. As multikinase inhibitors, the antitumour activity of regorafenib and sorafenib could extend beyond their antiangiogenic properties to a direct effect on tumour and stromal cells that modulate inflammatory and immune processes.[28] Recent phase 3 trials in HCC assessing multikinase inhibitors having profiles that partly overlap with regorafenib have failed to improve outcomes over sorafenib or versus placebo after sorafenib.[6–8,11] The results of this study suggest that the sequential use of two multikinase inhibitors with partly overlapping target profiles provides a survival benefit in HCC. Regorafenib has been shown to improve survival in patients with gastrointestinal stromal tumours after failure of two multikinase inhibitors (imatinib and sunitinib).[19]

This study was designed to assess a new systemic treatment for patients with HCC progressing on first-line therapy and incorporated lessons from previous phase 3 trials that failed to meet their primary endpoint.[6–14] Only patients with Child-Pugh A liver function were included to avoid the potential confounding effect of impaired liver function on survival. To ensure that treatment groups were balanced with respect to relevant prognostic factors, randomisation was stratified by α-fetoprotein concentrations and ECOG performance status. However, unlike in previous studies,[4,11] macrovascular invasion and extrahepatic disease were separate stratification factors. We also stratified for geographical region because of differences in access to cancer care and the use of locoregional therapies. Although the trial was not stratified for aetiology, geographical region accounts partly for the aetiology of HCC because hepatitis B virus infection is the

predominant underlying cause of HCC in most Asian countries.

The safety of regorafenib in HCC in this study is consistent with the safety profile of regorafenib in other gastrointestinal malignancies, and with no new safety concerns.[18,19] The most common grade 3 or 4 adverse events included hypertension, hand–foot skin reaction, fatigue, and diarrhoea. Exclusion of patients who were unable to tolerate sorafenib could have reduced the occurrence of severe adverse events; 10% of patients discontinued treatment due to a regorafenib-related adverse event. Although underlying liver dysfunction is expected to be more common in patients with HCC, the rates of liver-related adverse events and liver failure in the regorafenib group were not higher in this study compared with in other regorafenib trials.[18,19] In this study, the only two cases of drug-related death due to liver failure occurred in the placebo group. Although adverse events in the regorafenib group led to higher rates of treatment interruptions and dose reductions than did those in the placebo group, the median treatment duration was longer with regorafenib than with placebo. Assessments using standard, validated measures of quality of life in patients with hepatobiliary cancer showed no clinically meaningful differences between the groups.

Although biomarker-based treatment decisions have become standard of care in certain tumour types, no baseline markers predictive of treatment benefit have been identified for patients with HCC.[29,30] Exploratory studies have suggested that there is an association between certain adverse events, most notably hand–foot skin reaction, and overall survival and time to progression.[31] However, because this approach is based on post-randomisation events, it does not inform the selection of patients who could derive a greater treatment benefit.

A potential limitation of the study is that it was undertaken in patients who progressed during previous sorafenib treatment, and therefore firm conclusions about the efficacy of regorafenib in patients who do not tolerate sorafenib cannot be drawn. In addition, special populations, such as patients co-infected with HIV, are not included here.

The results of this study represent a significant advance in addressing an unmet need in the treatment of HCC. All previous second-line trials of novel agents have failed;[11–14] thus no effective systemic therapies after progression on sorafenib are currently available. These data underscore that prolonging exposure to multikinase inhibitors such as the sequence of sorafenib and regorafenib in conjunction with proper management of adverse events can lead to an extension in survival. In conclusion, this study met its primary endpoint showing that regorafenib improves overall survival in patients with HCC who had disease progression during first-line treatment with sorafenib.

Contributors

JB, M-AL, RSF, and GMe conceived and designed the study. JB, SQ, PM, AG, Y-HH, GB, MP, OY, OR, VB, RG, GMa, PJR, TS, J-PB, IO-H, MK, A-LC, JML, RSF, M-AL, AB, GMe, and GH collected the data. JB, M-AL, AB, and GMe analysed and interpreted the data. All authors participated in the drafting, review, and approval of the report and in the decision to submit for publication.

Declaration of interests

JB has received grants and personal fees from Bayer; consultancy and advisory fees from Bayer and Novartis; and consultancy fees from Gilead, AbbVie, Kowa, BTG, ArQule, Terumo, Bristol-Myers Squibb, Boehringer Ingelheim, OSI, Roche, Eisai, Sirtex, and Onxeo. PM has received consultancy fees from Bayer. OY has received grants from Gilead Sciences, MSD, Bayer, Mitsubishi Tanabe Pharma, and Bristol-Myers Squibb. OR has received personal fees from Transgene and Bristol-Myers Squibb. VB has received personal fees from Bayer, Boehringer Ingelheim, Pfizer, MSD, and Roche; and non-financial support from Boehringer Ingelheim, Pfizer, and MSD. RG has received advisory fees from Bayer France. PJR has received personal fees from Bayer, Celgene, Roche, Merck, and Sirtex; advisory fees from Bayer, Baxalta, Amgen, and Sanofi; speaker fees from Celgene; and support for attending meetings from Bayer, Celgene, and Merck. J-PB has received grants from Bayer during the conduct of the study and lecturing and consultancy fees from Bayer. IO-H has received grants and personal fees from Bayer; personal fees from Gilead, Intercept, Daiichi Sankyo, AbbVie, and Boehringer Ingelheim; grants from Lilly; and non-financial support from Gilead, MSD, and AbbVie. MK has received grants from Chugai, Otsuka, Takeda, Taiho, Sumitomo Dainippon, Daiichi Sankyo, MSD, Eisai, Bayer, and AbbVie; lecturing fees from Bayer, Eisai, MSD, and Ajinomoto; and advisory and consultancy fees from Bayer, Eisai, Kowa, MSD, Bristol-Myers Squibb, Chugai, and Taiho. A-LC has received consultancy fees from Novartis, Eisai, MSD, Bayer, Ono Pharmaceuticals, Bristol-Myers Squibb, and Merck Serono. JML has received grants from Bayer, Bristol-Myers Squibb, Blueprint Medicines, and Boehringer Ingelheim; and consultancy fees from Bayer, Bristol-Myers Squibb, Blueprint Medicines, Boehringer Ingelheim, Lilly Pharmaceuticals, Celsion, Biocompatibles, and Novartis. RSF has received grants, consultancy fees, and travel support from Bayer, Pfizer, Novartis, and Bristol-Myers Squibb. M-AL is an employee of Bayer. AB is an employee of Bayer. GMe is an employee of Bayer and owns stock in Bayer. GH has received a grant and advisory board and speaker fees from Bayer. SQ, AG, Y-HH, GB, MP, GMa, and TS declare no competing interests.

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